NEOADJUVANT CHEMOTHERAPY INFUSION IN THE ARM IPSILATERAL TO BREAST CANCER INCREASES THE RISK OF LYMPHEDEMA AMONG WOMEN SUBJECTED TO AXILLARY LYMPHADENECTOMY

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Abstract

Background: Adjuvant chemotherapy (CT) infusion in the ipsilateral upper limb (IA) increases the risk of lymphedema (LE). The risk attributed to neoadjuvant CT (NAC) infusion in the IA remains unknown. We aimed to evaluate the association of NAC and/or adjuvant CT infusion in the IA with axillary lymphadenectomy (AL) and the occurrence of LE secondary to breast cancer (BC) treatment.

Methods: A prospective cohort study of 683 women subjected to AL and treated with NAC and/or adjuvant CT for BC. The patients were evaluated before treatment, immediate and every 6 months after surgery. Cumulative incidence and population attributable risks of LE were calculated.

Results: 8-year cumulative incidence of LE was 33.1%. NAC and CT infusion and infusion of >2 cycles into the IA respectively increased by 1.68, 1.67 and 1.78 times the risk of LE respectively (all $P<0.01$). LE could be avoided in 9.4% of cases if the CT infusion had not been administered in the IA.

Conclusions: 33.1% of women developed LE. The risk of LE was notably increased among women who received CT in the IA. Avoidance of NAC or adjuvant CT in the IA could prevent 9% of the LE cases observed in this population.

Keywords: Lymphedema, Breast Neoplasm, Chemotherapy, Neoadjuvant, Surgery breast cancer.

Introduction

Lymphedema is the most feared side effect that may follow axillary lymphadenectomy in patients treated for breast cancer (BC). The 5-year cumulative incidence of lymphedema (LE) secondary to BC treatment in patients subjected to axillary lymphadenectomy is 30.3%,[1] while the risk of lymphedema among patients subjected only to sentinel lymph node biopsy is 4 times lower than that among patients who undergo complete lymphadenectomy.[2]
Approximately 30–40% of BC patients present with axillary metastasis (cN1) at initial diagnosis.[3] The presence of metastasis in axillary lymph nodes remains one of the primary factors that indicates systemic treatment, particularly chemotherapy, among BC patients. Neoadjuvant chemotherapy has been administered to cN1 patients. The current rates of complete lymph node pathological response to neoadjuvant chemotherapy schemes depend on the molecular subtype, and thus, they range from 15% to 70%.[4, 5] This type of approach has allowed many cN1 patients to be spared from axillary lymphadenectomy, which decreases their risk for lymphedema. Some prospective studies that have addressed the possibility of performing only sentinel lymph node biopsy in cN1 patients after neoadjuvant chemotherapy have shown promising results.[6, 7] However, many patients, even after neoadjuvant chemotherapy, will require complementary axillary lymphadenectomy.
The use of totally implantable venous-access ports (TIVAPs) is very common. More than 400,000 TIVAPs are sold annually in the USA.[8] Although its use is widespread, its implementation is subject to high rates of complications, such as pneumothorax (1–4%), hemothorax (1–11%), arterial puncture (0–15%), cardiac arrhythmias (23–25%), arrhythmias that require cardioversion (0.9%) and pericardial tamponade (up to 10%). Other late complications may occur, including infection (2.4–16%), thrombosis (1–56%) and extravasation (0.5–6%).[9] Some patients and healthcare teams prefer the use of peripheral veins for chemotherapy infusion, which is most likely due to these potential complications and high cost.
Many patients who are subjected to neoadjuvant chemotherapy receive chemotherapy infusion in the limb ipsilateral to the tumor site because an axillary approach that contraindicates such a procedure has yet to be developed.
We found no prospective cohort study that has specifically addressed the impact of neoadjuvant chemotherapy infusion in the IA on the increased risk for lymphedema. Using a prospective cohort study that is specifically designed to assess the risk of lymphedema, we aimed to analyze the risk of upper limb lymphedema after lymphadenectomy associated with chemotherapy infusion in the ipsilateral limb.

Objective

To evaluate the association between chemotherapy infusion in the limb ipsilateral to axillary lymphadenectomy and the occurrence of lymphedema secondary to BC treatment.

Methods

A prospective cohort study was conducted in women diagnosed with BC at a single cancer treatment center located in Rio de Janeiro, Brazil. The methodological details of this study have been published.[1] This study was approved by the ethics committee of the Brazilian National Cancer Institute (Instituto Nacional de Câncer –INCA) (42/02), and all patients provided informed consent.
Only women who presented from August 2001 to November 2002 with an indication for axillary lymphadenectomy and neoadjuvant and/or adjuvant chemotherapy were included in this study. Women with bilateral breast cancer, a prior history of cancer, prior functional or

lymphatic changes in the upper limbs, those cognitively unable to answer the questions and those who require a walking aid, were excluded from the study.
Data were collected by in-person interview, physical examination and medical chart review. The patients were evaluated before the first cancer treatment, in the immediate postoperative period and every 6 months after surgery. At each appointment, upper limb volumetry was performed according to the study protocol. The date of the last follow-up appointment was December 2012.
The occurrence of lymphedema, which is defined as a difference ≥200 ml between the ipsilateral and the contralateral upper limbs, as assessed in the physical examination by circumference measurements, was considered the outcome. Limb volume was calculated using the truncated cone formula.[10]
Chemotherapy infusion in the upper limb ipsilateral to BC was considered the primary exposure. This information was gathered from the medical records and was categorized according to the number of cycles administered. The chemotherapy regimens used included no taxanes due to the institutional protocol in use during patient recruitment.
Data on the following variables were collected at the time of cancer diagnosis and were used to describe the study population and to control for possible confounding variables in the association between chemotherapy infusion and lymphedema: age, marital status, education, main occupation, nutritional status, BC side and clinical stage. Clinical and treatment data were also collected, such as: type of breast surgery, whether breast reconstruction was performed, axillary lymphadenectomy level, number of removed and compromised lymph nodes, whether radiation therapy or hormone therapy was given and the incidence of postoperative complications (e.g., seroma, necrosis, surgical wound infection, axillary web syndrome, intercostobrachial nerve injury and winged scapula).
Descriptive analysis was performed using the mean and standard deviation for the quantitative variables and the frequency distribution for the qualitative variables. The chi-square test was used to compare the frequency of demographic and clinical variables to assess differences between chemotherapy administered in the ipsilateral limb and chemotherapy that was not. A Kaplan-Meier analysis was used to assess the cumulative incidence of lymphedema during the follow-up time and the lymphedema onset time, and the log-rank test was used to assess differences in exposure between the curves. The risk for the development of lymphedema was calculated by univariate and multiple Cox regression, and the variables for which $p<0.20$ were selected to fit the multivariate model. Significance was set at $p<0.05$ for all tests.
To determine the percentage of lymphedema that could be prevented in the population by avoiding chemotherapy in the limb ipsilateral to breast cancer, the population attributable risk (PAR) was assessed using the following formula: $PAR=Pr(E)(HR-1)/1+[P(E)(HR-1)]$, where P(E) is the probability of events among the exposed individuals, and the HR is the adjusted hazard ratio.[11]
The statistical software package SPSS IBM®, version 23.0, was used for all analyses. There was no funding source for this study.

Results

A total of 683 women were included in this study and were followed for an average of 5.1 years (3.5 SD). At the time of BC diagnosis, most were women younger than 65 years of age (86.8%), single (50.2%), had an incomplete primary education (67.3%) and listed housekeeping as their main occupation (57.3%). In all, 66.9% women were classified as

overweight or obese. Advanced clinical stage (≥IIB) was predominant (56.2%), and most women underwent mastectomy (70.8%).
The most widely used chemotherapy regimen included the use of both neoadjuvant and adjuvant adriamycin and cyclophosphamide (AC) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) chemotherapy (80.9%). Chemotherapy infusion in the upper limb ipsilateral to BC was performed in 38.9% women, of whom 73.3% were subjected to neoadjuvant, 22.2% were subjected to adjuvant chemotherapy, and 4.5% were subjected to both neoadjuvant and adjuvant chemotherapy. On average, 3.33 (1.7 SD) infusions were administered among the women subjected to chemotherapy infusion in the limb.
The demographic and clinical characteristics of the patients, which are outlined in Table 1, illustrate the differences between chemotherapy given in the limb ipsilateral to BC and chemotherapy that was not. The women with lower education ($p=0.017$), those subjected to neoadjuvant chemotherapy ($p<0.001$), those who did not receive AC and/or FAC chemotherapy regimens ($p<0.001$), those subjected mastectomy ($p<0.001$) and those with clinical stage ≥IIB ($p<0.001$) were more frequently exposed to chemotherapy infusion in the ipsilateral limb.
During the follow-up period, 33.1% of women developed lymphedema, with a mean onset time of 8.0 years (95% CI 7.7–8.4). Table 2 outlines the incidence of and the time to develop lymphedema to assess the differences between chemotherapy that was administered in the limb ipsilateral to BC and chemotherapy that was not. A higher incidence of lymphedema was observed among women subjected to chemotherapy in the ipsilateral limb ($p=0.003$) with a median lymphedema onset time of 6.9 years ($p<0.001$; Figure 1 A). A higher incidence of lymphedema was also observed among those who received 2 or more cycles of chemotherapy performed in the ipsilateral limb ($p<0.001$; Figure 1 B), those who received neoadjuvant chemotherapy infusion ($p<0.001$; Figure 1 C) and those who did not receive AC or FAC chemotherapy ($p=0.007$; Figure 1 D).
The supplemental table outlines the association between lymphedema and the demographic and clinical variables; the variables for which $p<0.020$ were selected to fit the model. Chemotherapy infusion in the limb ipsilateral to BC increased the risk of lymphedema by 1.67 times ($p<0.001$) when the effect of possible confounding variables was removed. The analysis according to the number of cycles showed that women subjected to more than 2 cycles of chemotherapy in the ipsilateral limb had a 1.78 times greater risk of lymphedema ($p<0.001$), which caused a 14% increase in risk at each cycle administered to the ipsilateral arm ($p<0.001$). Regarding the type of chemotherapy, those who received neo-adjuvant chemotherapy infusion in the ipsilateral limb had a 1.68 times greater risk of lymphedema ($p=0.002$; Table 1).
The calculation of the attributable fraction showed that 9.4% of lymphedemas cases could have been avoided if chemotherapy infusion had not been performed in the limb ipsilateral to BC. The analysis according to the number of cycles showed that 9.3% of lymphedema cases could have been prevented if 2 or more cycles of chemotherapy had not been administered in the ipsilateral arm. Regarding the type of chemotherapy, 8.4% of lymphedema cases could have been prevented if chemotherapy infusion had not been administered in the limb ipsilateral to BC (Table 1).

Discussion

Currently, physicians have a strong tendency to prescribe neoadjuvant chemotherapy to patients with BC, especially patients with cN1 disease, which decreases the need for axillary lymphadenectomy after complete pathological response of sentinel lymph nodes with and

without marking clips. The results from the most recent prospective studies are quite encouraging for this type of approach.[6, 7] However, many patients, even after neoadjuvant chemotherapy, still require complementary axillary lymphadenectomy. Furthermore, the subset of patients who will demonstrate a complete response in the lymph nodes cannot be safely predicted. Thus, any approach that decreases the risk of LE after axillary lymphadenectomy is extremely important. Many patients today still receive neoadjuvant chemotherapy infusion in the limb ipsilateral to the tumor site and where lymphadenectomy will potentially be performed.

In the present study, we specifically evaluated the association between chemotherapy infusion in the limb ipsilateral to axillary lymphadenectomy and the occurrence of LE.

The long-term risk of LE in our prospective cohort was 33.1%. The incidence of BC lymphedema reported in one meta-analysis was 21.4% in prospective studies, although most of these studies had a short follow-up time.[2] The study by Petrek et al.,[12] although it was retrospective, had a 20-year follow-up and showed a 49% incidence of BC lymphedema, which suggests that time itself may be a risk factor for lymphedema among those patients. In our study, we observed a long mean onset time for LE (8.05 years (95% CI 7.69–8.41)). The mean onset time for LE in patients who received chemotherapy in the ipsilateral limb was significantly shorter than that in patients who did not (6.92 years versus 8.69 years, $p<0.001$). The LE onset time was also significantly shorter among patients who received 2 or more cycles of chemotherapy in the ipsilateral limb ($p<0.001$). Similarly, the LE onset time was shorter among patients who received neoadjuvant chemotherapy ($p<0.001$).

Several risk factors associated with LE have already been described,[2] and these include a high body mass index, treatment with radiation therapy, radical nature of axilla and breast surgery, the number of dissected lymph nodes and age.[2] Few studies associated chemotherapy as an independent risk factor of LE.[1, 13, 14]

In the study by Norman et al.,[13] 81% patients received anthracycline-based chemotherapy regimens. The HR among the patients treated with and without chemotherapy was 1.46 (95% CI, 1.04–2.04). Patients who received a combination of axillary lymphadenectomy and chemotherapy had a risk of LE that was 4.16 times (HR 4.16; 95% CI, 1.32–12.45) greater than that of patients who did not undergo chemotherapy or radiation therapy and received only sentinel node biopsy.[13]

In a retrospective study, Shih, et al. [14] showed an increase in the risk of LE associated with chemotherapy over a 4-year follow-up, with an OR of 1.83 (95% CI 1.14–2.95), compared with the group that did not undergo chemotherapy.

In 2012, we published the data from our complete patient cohort (n=1054). In that study, we included nomograms that were used to calculate the 5-year risk of LE. Neoadjuvant and/or adjuvant chemotherapy in the ipsilateral limb were also independent risk factors for LE ($p<0.0001$).[1]

Conversely, Huang, et al. [15] showed a decrease in the risk of LE associated with neoadjuvant chemotherapy, with a HR of 0.62 (95% CI 0.39–0.98). This study, however, may have some limitations due to its design. This was a cross-sectional study of 230 patients that used a self-reporting questionnaire administered by phone.

In a retrospective study, Hayes et al.,[16] demonstrated a positive association between systemic treatment and the risk of LE. However, in that study, the impact of LE was apparently more associated with hormone therapy (tamoxifen) use than with chemotherapy use.

We found no study in the literature that specifically assessed the risk of LE with respect to chemotherapy administered in the limb (ipsilateral or contralateral) and the number of cycles of chemotherapy in the ipsilateral limb. This type of analysis was only possible because our

cohort was specifically designed for the study of LE. All data were collected prospectively and were pre-determined, and therefore, our findings are rather distinct compared with those of other previously published studies.

In the present study, we selected only patients after a 10-year follow-up who underwent chemotherapy and axillary lymphadenectomy as part of their BC treatment. Chemotherapy infusion in the limb ipsilateral to BC increased the risk of LE by 67% (1.67 HR; 95% CI 1.27–2.19; p<0.001). Patients who received more than 2 cycles in the ipsilateral limb had a 78% greater risk of LE (1.78 HR; 95% CI 1.32–2.39; p<0.001) than patients who did not receive chemotherapy in the ipsilateral limb. The risk of lymphedema increased by 14% (1.14 HR; 95% CI 1.06–1.22; p<0.001) with each additional infusion in the ipsilateral limb when the number of continuous cycles (0 to 9 cycles) was analyzed.

Regarding the type of chemotherapy administration in the ipsilateral limb, neoadjuvant chemotherapy (alone or combined with adjuvant chemotherapy) increased the risk of lymphedema by 68% compared with patients who did not receive chemotherapy in the ipsilateral limb (HR 1.68; 95% CI 1.201–2.35; p<0.001). Conversely, no increase was observed in the risk of LE between those who received adjuvant chemotherapy in the ipsilateral limb and those who did not (p=0.349). In the multivariate model, when patients who received only adjuvant chemotherapy in the ipsilateral limb were included as a reference, the risk of lymphedema was found to be 2.32 times greater in these patients than in patients who received neoadjuvant chemotherapy in this limb (p=0.005).

In a prospective study, Jung et al.,[17] studied 848 patients, all of whom received chemotherapy and axillary lymphadenectomy as part of their BC treatment. A total of 552 of those patients received adjuvant chemotherapy, and 296 patients received neoadjuvant chemotherapy. LE was objectively defined according to a single circumference measurement of the limb and was subjectively defined based on patient perception. The median follow-up time of these patients was 5.1 years. The use of taxane was an independent risk factor of LE with a HR of 2.07 (95% CI 1.03–4.15), which was similar to the use of neoadjuvant chemotherapy with a HR of 1.39 (1.05–1.84). Unfortunately, this study failed to specify the laterality and the number of chemotherapy infusions in each limb (ipsilateral or contralateral).[17]

In a retrospective study of 313 patients with clinically positive axilla who underwent chemotherapy and axillary lymphadenectomy, Kim, et al. [18] found no differences in LE incidence between patients who were subjected to exclusive neoadjuvant chemotherapy (n=133) and those who were subjected to neoadjuvant and adjuvant chemotherapy (n=180).

In a prospective study of 229 patients who underwent unilateral axillary lymphadenectomy and chemotherapy, Specht, et al. [19] compared the incidence of LE in the group that was subjected to neoadjuvant chemotherapy (n=68) with another group that was subjected to adjuvant chemotherapy (n=229). The authors found no significant differences in LE incidence between the two groups, with an HR of 0.74 (95% CI 0.37–1.48; p=0.39). However, they found a 9 times greater risk for the development of lymphedema among patients who received neoadjuvant chemotherapy and maintained residual lymph node disease.[19]

Swaroop, et al. [20] aimed to examine the relationship between taxane-based chemotherapy and mild and chronic upper limb edema and to determine the type of taxane that affects the risk of lymphedema. They found no association between taxane-based chemotherapy with lymphedema, although they did find an increased risk of mild edema among patients who received docetaxel.[20]

In a retrospective study, Cariati, et al. [21] analyzed the impact of chemotherapy on the risk of lymphedema in 273 patients with positive axilla who were subjected to unilateral axillary lymphadenectomy. Of all the patients, 186 received chemotherapy, and 87 did not. Of the

patients who received chemotherapy, 69 received neoadjuvant chemotherapy, 115 received adjuvant chemotherapy, and 2 received both (neoadjuvant + adjuvant chemotherapy). Of the 69 patients who received neoadjuvant chemotherapy, 64 received taxane, and of the 115 patients who received adjuvant chemotherapy, 90 received taxane. Of the 2 patients who received both regimens, only 1 received taxane. After a follow-up of 2.67 years, the incidence of LE was 27.1% (74/273). Taxane administration was strongly associated with the development of LE, which was diagnosed in 33.5% of the 155 women who received taxane-based chemotherapy. According to the multivariate analysis, the patients who received taxane had a HR of 2.83 (95% CI 1.31–6.06) for the development of LE compared with those who did not receive chemotherapy. No increase was found in the risk of LE among patients who received neoadjuvant taxane-based chemotherapy.[21]

Peripheral edema associated with taxane use is fairly well known.[22, 23] This type of edema is more commonly found in the upper and lower limbs, although it may be generalized. It apparently results from the cumulative dose of taxane associated with the combined use of corticosteroids, which are given to reduce the systemic side effects of chemotherapy.[24, 25] A suggested mechanism of action is the increase in capillary permeability induced by endothelial exposure to taxane and the progressive accumulation of proteins in the interstitial space.[26, 27] Some studies, however, have shown that this chemotherapy-related edema is transient.[28, 29]

In our multivariate Cox model, no increase was observed in the risk of LE in regimens that included anthracyclines and those that did not. Current (adjuvant and neoadjuvant) chemotherapy regimens include taxanes. This may be a limitation of our study because our results are based on a relatively old cohort of patients who were treated when taxanes were not routinely used. In our opinion, although it is plausible, the pathophysiology proposed above would fail to explain the long-term onset of LE because chemotherapy-related edema is transient. Therefore, the impact on the etiology of LE that is specifically attributed to the type of chemotherapy would be weaker.

We prefer to explain the chemotherapy-related LE in a different way. The physiology of the lymphatic system itself, described by Taylor,[30] could justify other effects of a chemotherapeutic agent on the venous system of the ipsilateral limb as a contributing factor in the etiology of LE. The direct action of the chemotherapeutic agent would lead to a chronic and permanent thickening of the venous wall, and therefore, to decreased venous compliance, which would lead to a relative increase in hydrostatic pressure in the venous capillaries (venules). This increase in pressure would in turn decrease the difference in pressure between the arteriolar system (high pressure) and the venous capillaries (low pressure) and would lead to a decreased interstitial fluid resorption by the venous system. Combined with the lymphatic drainage deficit of the lymphatic system, this decreased resorption could occur as a result of the lymphadenectomy and would lead to a greater interstitial fluid accumulation, thereby causing LE.

Therefore, we may conclude that neoadjuvant chemotherapy infusion in the limb ipsilateral to the tumor among patients who will (or may) be subjected to axillary lymphadenectomy significantly increases the long-term risk of lymphedema. A total of 9% of lymphedema cases that result from axillary lymphadenectomy could be prevented by avoiding chemotherapy infusion in the ipsilateral limb. The use of the contralateral limb or implantable catheters may decrease this risk. We found no significant association between the use of anthracyclines and the risk of LE. However, other studies have shown some correlation of LE with taxane use, which, if confirmed, could theoretically further increase the risk if infused into the ipsilateral limb.

Conclusion
During the follow-up period, 33.1% of women with BC subjected to axillary lymphadenectomy developed lymphedema. The risk of lymphedema was noticeably increased among patients who received chemotherapy in the limb ipsilateral to the tumor site. Avoidance of chemotherapy in the limb could prevent 9% of lymphedema cases observed in this population.

Declaration of interests
The authors have no conflicts of interest to declare.

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Table 1 – Demographic and clinical characteristics according to whether or not patients received chemotherapy in the arm ipsilateral to breast cancer (n=683)

Variable	Infusion of chemotherapy in the ipsilateral arm*		
	No (n=417) n (%)	Yes (n=266) n (%)	p value
Age (at breast cancer diagnosis)			
<65 years	358 (85.9)	235 (88.3)	0.347
≥65 years	59 (14.1)	31 (11.7)	
Marital status			
Living without partner	201 (48.4)	139 (53.1)	0.269
Living with partner	214 (51.6)	123 (46.9)	
Education level			
Low (<8 years)	258 (63.9)	185 (72.8)	0.017
High (≥8 years)	146 (36.1)	69 (27.2)	
Main occupation			
Home activities	178 (56.5)	117 (58.5)	0.656
Work outside the home	137 (43.5)	83 (41.5)	
Nutritional status			
Overweight or obese	288 (69.1)	169 (63.5)	0.134
Normal	129 (30.9)	97 (36.5)	
Type of CT in the ipsilateral arm			
Neoadjuvant	02 (0.5)	94 (35.3)	<0.001
Adjuvant	412 (98.8)	58 (21.8)	
Neo and Adjuvant	03 (0.7)	114 (42.9)	
CT with AC or FAC			
No	48 (11.5)	82 (30.9)	<0.001
Yes (Neo and/or adjuvant)	369 (88.5)	183 (69.1)	
Side of Surgery			
Right	198 (47.5)	125 (47.0)	0.901
Left	219 (52.5)	141 (53.0)	
Type of breast surgery			
Mastectomy	237 (57.50)	242 (91.3)	<0.001
Breast conservation	175 (42.5)	23 (8.7)	
Clinical Stage			
≥IIB	190 (45.9)	192 (72.2)	<0.001
<IIB	224 (54.1)	74 (27.8)	
*The differences correspond to missing values			

Table 2 – Cumulative incidence and time to the development of lymphedema according to whether or not patients received chemotherapy in the arm ipsilateral to breast cancer (n=683)

Chemotherapy in the ipsilateral arm	Lymphedema n (%)			Time (years) to the development of lymphedema		
	No	Yes	p value*	Mean	(95% CI)	p value**
Infusion of CT in the ipsilateral arm						
No	297 (71.2)	120 (28.2)	0.003	8.7	(8.3–9.1)	<0.001
Yes	160 (60.2)	106 (39.8)		6.9	(6.3–7.5)	
Number of cycles of CT in the ipsilateral arm						
None	297 (71.2)	120 (28.8)	0.001	8.69	(8.3–9.1)	<0.001
1 cycle	44 (73.3)	16 (26.7)		8.83	(7.8–9.9)	
2 or more cycles	90 (56.3)	90 (43.7)		6.33	(5.6–7.1)	
Type of CT in the ipsilateral arm						
CT not administered in ipsilateral arm	297 (71.2)	120 (28.2)	<0.001	8.69	(8.3–9.1)	<0.001
CT neo adjuvant in the ipsilateral arm***	115 (55.6)	92 (44.4)		6.21	(5.5–6.9)	
CT adjuvant in the ipsilateral arm	45 (76.3)	14 (23.7)		9.16	(3.2–9.1)	
CT with AC or FAC						
No	79 (60.8)	51 (39.2)	0.101	7.02	(6.1–7.9)	0.007
Yes (Neo and/or adjuvant)	377 (68.3)	175 (31.7)		8.05	(7.9–8.6)	

*Chi-square test; **Log-Rank test; ***With or without adjuvant CT
CI=Confidence interval; CT=Chemotherapy; AC=Adriamycin and Cyclophosphamide; FAC=5-Fluorouracil, Doxorubicin, Cyclophosphamide

Table 3 – Infusion of chemotherapy in the arm ipsilateral to breast cancer and the risk of lymphedema (n=683)

Infusion of chemotherapy in the ipsilateral arm	Crude		Adjusted		PAR*
	HR (95% CI)	p value	HR (95% CI)	p value	
Infusion of CT in the ipsilateral arm					
No	Reference		Reference		
Yes	1.90 (1.46–2.47)	<0.001	1.67 (1.27–2.19)[a]	<0.001	
Number of cycles of CT in the ipsilateral arm					
None	Reference		Reference		
1 cycle	0.92 (0.54–1.54)	0.743	0.93 (0.55–1.56)[b]	0.774	*
2 or more cycles	2.36 (1.79–3.11)	<0.001	1.78 (1.32–2.39)[b]	<0.001	9.3%
Infusion of CT in the ipsilateral arm					
Number of cycles (continuous)	1.22 (1.14–1.30)	<0.001	1.14 (1.06–1.22)[b]	<0.001	**
Type of CT in the ipsilateral arm					
CT not given in the ipsilateral arm	Reference		Reference		
CT neo adjuvant in the ipsilateral arm***	2.44 (1.86–3.22)	<0.001	1.68 (1.201–2.35)[c]	0.002	8.4%
CT adjuvant in the ipsilateral arm	0.78 (0.45–1.36)	0.387	0.77 (0.44–1.34)[c]	0.349	*
CT with AC or FAC					
Yes (Neo and/or adjuvant)	Reference		Reference		
No	1.53 (1.12–2.08)	0.008	1.23 (0.99–1.69)[c]	0.214	*

HR=Hazard Ratio; PAR=Population Attributable Risk; CI=Confidence interval; CT=Chemotherapy; AC=Adriamycin and Cyclophosphamide; FAC=5-Fluorouracil, Doxorubicin, Cyclophosphamide

[a] Adjusted for nutritional status, radiotherapy and seroma

[b] Adjusted for nutritional status, clinical stage and radiotherapy;

[c] Adjusted for nutritional status, clinical stage, radiotherapy and seroma

*Only performed for statistically significant associations (p<0.05)

**Not calculable

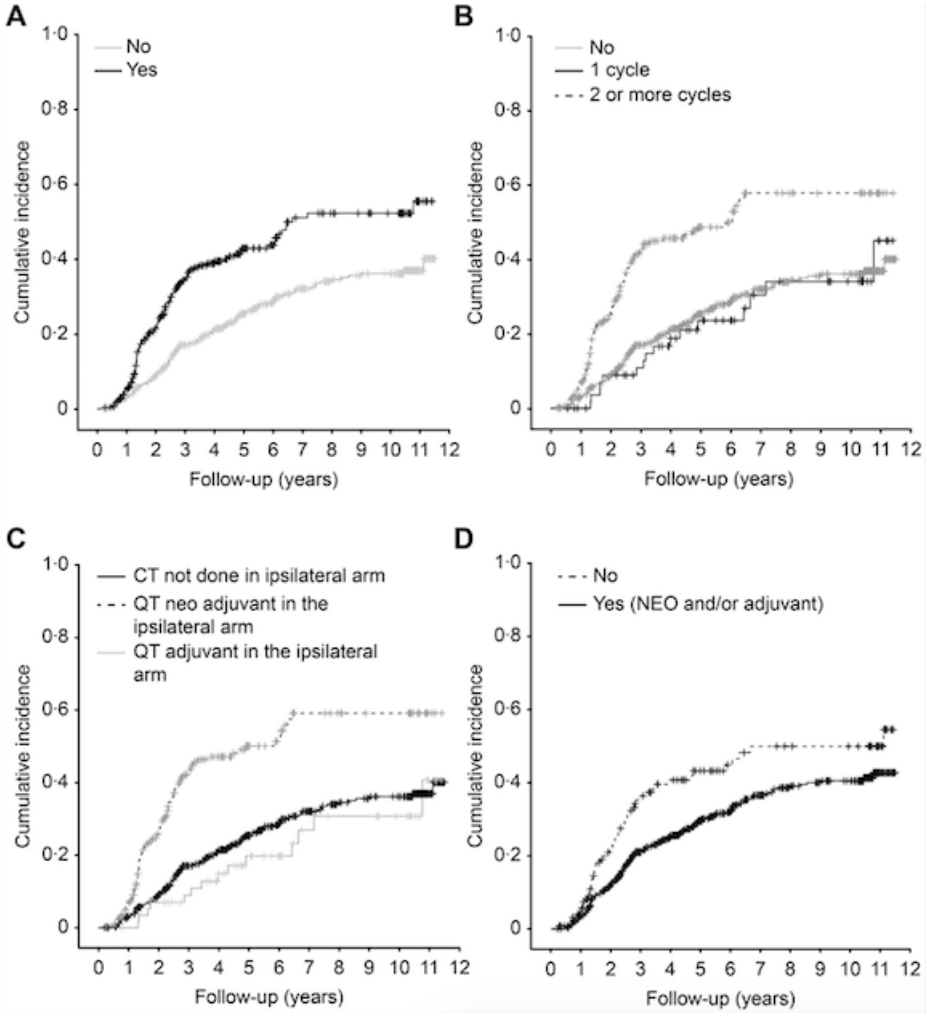
***With or without adjuvant CT

Supplemental Table – Univariate Cox regression analysis between the demographic and clinical characteristics and the risk of lymphedema (n=683)

Variables	HR (95% CI)	p value
Education level		
Low	Reference	**0.111**
High	1.27 (0.95–1.69)	
Main occupation		
Work outside of the home	Reference	0.863
Home activities	1.03 (0.76–1.39)	
Nutritional status		
Normal	Reference	**0.028**
Overweight or obese	1.39 (1.03–1.86)	
Body Mass Index		
Continuous	1.05 (1.02–1.07)	**<0.001**
Obese		
No	Reference	**0.012**
Yes	1.40 (1.07–1.83)	
Age (at breast cancer diagnosis)		
<65 years	Reference	0.299
≥65 years	1.23 (0.83–1.80)	
Age (at breast cancer diagnosis)		
Continuous	1.01 (0.99–1.02)	0.269
Type of breast surgery		
Breast conservation	Reference	**0.002**
Mastectomy	1.63 (1.20–2.22)	
Breast reconstruction		
No	Reference	**0.198**
Yes	0.66 (0.35–1.24)	
Axillary lymphadenectomy		
Partial	Reference	0.639
Total	0.89 (0.55–1.44)	
Number of lymph nodes removed		
<15 lymph nodes	Reference	0.911
≥15 lymph nodes	1.02 (0.76–1.36)	
Number of lymph nodes removed		
Continuous	1.00 (0.98–1.02)	0.969
Positive lymph nodes (pN)		
No	Reference	**0.011**
Yes	1.42 (1.09–1.87)	
Number of positive lymph nodes		
Continuous	1.02 (1.00–1.03)	**0.008**
Stage		
<II B	Reference	**<0.001**
≥II B	1.79 (1.36–2.36)	
Radiotherapy		
No	Reference	

Yes	2.32 (1.66–3.25)	**<0.001**
Axillary radiotherapy		
No	Reference	**<0.001**
Yes	3.13 (2.40–4.09)	
Hormone therapy		
No	Reference	0.590
Yes	0.92 (0.69–1.23)	
CT with AC or FAC		
No	Reference	0.008
Yes (Neo and/or adjuvant)	1.53 (1.12–2.09)	
Seroma		
No	Reference	**0.013**
Yes	1.43 (1.08–1.89)	
Necrosis		
No	Reference	0.951
Yes	1.01 (0.77–1.32)	
Surgical wound infection		
No	Reference	0.676
Yes	1.09 (0.73–1.63)	
Axillary web syndrome		
No	Reference	**0.115**
Yes	0.80 (0.60–1.06)	
Paresthesia in the arm		
No	Reference	**0.122**
Yes	0.77 (0.56–1.07)	
Winged scapula		
No	Reference	0.240
Yes	1.19 (0.89–1.59)	
Bold values were selected for multiple regression analysis HR=Hazard Ratio; CI=Confidence interval; CT=Chemotherapy; AC=Adriamycin and Cyclophosphamide; FAC=5-Fluorouracil, Doxorubicin, Cyclophosphamide		

FIGURE 1



Lossy compression figure.

For the full-resolution image, please see the attached file

(A) Cumulative incidence of lymphedema according to patients who received chemotherapy infusion in the ipsilateral arm ($p<0.001$).
(B) Cumulative incidence of lymphedema according to the number of chemotherapy infusion cycles in the ipsilateral arm ($p<0.001$).
(C) Cumulative incidence of lymphedema according to the CT moment in the ipsilateral arm ($p<0.001$)
(D) Cumulative incidence of lymphedema according to the type of CT in the ipsilateral arm ($p=0.007$)